Iron is involved in prion disease-associated neuronal demise

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Imbalance of iron homeostasis is a common feature of prion disease-affected human, mouse, and hamster brains, according to a new study by Dr. Neena Singh and colleagues at Case Western Reserve University School of Medicine, alongside collaborators from Creighton University. These findings, published March 13 in the open-access journal *PLoS Pathogens*, provide new insight into the mechanism of neurotoxicity in prion disorders, and novel avenues for the development of therapeutic strategies.

Unlike other neurodegenerative conditions, prion disorders are sporadic, inherited, and infectious, and affect both humans and animals; common examples are mad cow disease in cattle, scrapie in sheep, and Creutzfeldt-Jakob disease in humans. The causative agent is a misfolded protein referred to as PrP-scrapie that replicates itself by changing the conformation of neighboring copies of the same protein, namely the prion protein. Aggregates of PrP-scrapie are toxic to brain cells and cause a spongy-like appearance in diseased brains.

Research from the Singh laboratory suggests that accumulation of PrP-scrapie alters the metabolism of iron in diseased brains. The imbalance of brain iron homeostasis worsens with disease progression, and is not an outcome of end-stage disease. Since iron is highly toxic when mismanaged, this condition is likely to contribute significantly to prion-disease-associated neurotoxicity. The likely cause of this condition is loss of normal function of the prion protein in cellular iron metabolism demonstrated recently by Singh and colleagues, combined with gain of

toxic function by the redox-active PrP-scrapie complex as shown in this report.

Singh and her team were surprised to find that prion disease-affected brains are iron deficient despite a significant increase in their overall iron content. The group concludes that ferritin, a major iron storage protein, co-aggregates with PrP-scrapie in diseased brains and sequesters bound iron in the complex, creating a state of apparent iron deficiency. The brain cells respond to this condition by increasing their level of iron uptake, thus creating a vicious cycle of increased iron uptake in the presence of increased iron.

These observations contribute to our understanding of how the prion agent causes neurotoxicity, and may enable the development of novel therapeutic strategies targeted at restoring brain iron homeostasis in prion disorders.

More information: Singh A, Isaac AO, Luo X, Mohan ML, Cohen ML, et al. (2009) Abnormal Brain Iron Homeostasis in Human and Animal Prion Disorders. *PLoS Pathog* 5(3): e1000336. doi:10.1371/journal.ppat.1000336, dx.plos.org/10.1371/journal.ppat.1000336

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